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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
12/010,071	08/14/97	DAVID E BROOK	000000-01

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18N2/0014

EXAMINER

LEUSA, S

ART UNIT

PAPER NUMBER

1811

DATE MAILED: 08/14/97

**Please find below and/or attached an Office communication concerning this application or proceeding.**

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This is a communication from the examiner in charge of your application.  
 COMMISSIONER OF PATENTS AND TRADEMARKS

DATE MAILED:

☒ This application has been examined    ☐ Responsive to communication filed on \_\_\_\_    ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 MONTHS from the date of this letter.  
 Failure to respond within the time period will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENTS ARE PART OF THIS ACTION:**

- |   |  |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948.                   |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449       | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474.     | 6. <input type="checkbox"/> _____  |

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-27 are pending in the application.  
 Of the above claims, \_\_\_\_ are withdrawn from consideration.
2. ☐ Claims \_\_\_\_ have been cancelled.
3. ☐ Claims \_\_\_\_ are allowed.
4. ☒ Claims 1-27 are rejected.
5. ☐ Claims \_\_\_\_ are objected to.
6. ☐ Claims \_\_\_\_ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on \_\_\_\_ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under 35 USC 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. \_\_\_\_; filed on \_\_\_\_.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☒ Other A FORMAL CLAIM of 119(c) priority for provisional is needed

**EXAMINER'S ACTION**

08/616,371

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### DETAILED ACTION

Claims 1-27 are currently pending and under consideration.

The Preliminary Amendment dated 5/15/97 in paper no. 8, was entered with the exception of page 4 of the amendment referring to the amendment to page 43, line 16 deleting "conditions" which was not found in the specification at the indicated location.

1. Applicant's election with traverse of Group IV, claims 9-21 and 23-27 in Paper No. 6 is acknowledged. However, applicant's traversal is moot since the restriction requirement, upon further search and reconsideration, is hereby withdrawn.
2. Claims 1-4, 6-21 and 23-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
  - A. The term "low" in claims 1-4, 11, 14, 15 and 17, is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. .
  - B. In claim 7, "selected for rapid entry into the target cell" lacks metes and bounds regarding the target cell and the means and prerequisites for selecting such an agent. Accordingly, the metes and bound of the "nitrosating agent" is not defined by the claim.
  - C. The term "rapid" in claim 7 is a relative term which renders the claim indefinite. The term "rapid" is not defined by the claim, nor does the specification provide a standard for ascertaining

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the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

✓ D. In claim 7, "the target cell" lacks clear antecedent basis.

✓ E. The method of claim 6 lacks metes and bounds as to the "disease or medical disorder" encompassed by the claimed method. Additionally, the method claim is indefinite for failure to state modes of administration and administrative amounts.

✓ F. In claim 8, line 2, "form" is misspelled.

✓ G. In claim 8, "the red blood cells" lack clear antecedent basis.

✓ H. In claims 9 and 12, "A preparation ... " is confusing as to whether a compound or composition is intended.

✓ I. In claim 15, the phrase "selected for the oxidation state of the heme iron and for the oxygen state" is indefinite as to the means and criteria for selection, improper antecedent basis for "the oxygen state" and confusion as to what oxidation state the phrase "the oxygen state" is referring to e.g. the heme iron or some other compound(s) oxidation state.

J. Method claims 15-27 are indefinite as to the mode of administration and the administrative amounts.

✓ K. In claims 20 and 21, "a form of SNO-Hb" is indefinite as to what form of Hb is encompassed within the metes and bounds of this claim.

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*Claim Rejections - 35 USC § 102*

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-3, 6-15, 18-21, 26 and 27 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

Stamler et al. discloses the therapeutic use of "low molecular weight" thiols, S-nitroso-protein and amino acid compounds (e.g. S-nitroso-hemoglobin or myoglobin) for regulating protein function, cellular metabolism including effecting vasodilation; increasing blood oxygen transport by hemoglobin and myoglobin; NO delivery; *in vitro* nitrosylation of molecules present in the body (e.g. see Abstract; pages 1-3 and claims). Stamler discloses a thionitrosylated

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hemoglobin composition (e.g. see page 58 and claims 13-16) comprising reacting hemoglobin in the presence of oxygen with a nitrosating agent (e.g. SNOAc) which composition anticipates that presently claimed. If equimolar amounts of nitrosating agent and Hb constitute “excess nitrosating agent” than the reference method anticipates the presently claimed method.

Alternatively optimizing nitrosylating amounts to achieve “excess” nitrosation of hemoglobin to insure nitrosylation of hemoglobin would be obvious to the skilled artisan at the time of applicant’s invention. The reference method of forming thionitrosylated oxygenated hemoglobin would either immediately envisage (e.g. anticipate) or alternatively render obvious the formation of thionitrosylate deoxygenated hemoglobin under anaerobic conditions as presently claimed. The reference specifically discloses the use of nitrosylated proteins (e.g. S-nitroso hemoglobin) and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims). The combination of nitrosating agents (e.g. thionitrosylated “Low” molecular weight and “high” molecular weight compounds; e.g. nitrosothiol, glutathione and hemoglobin) would be prima facie obvious to the skilled artisan at the time of applicant’s invention in order obtain the increased pharmaceutical effects of the agents.

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6. Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al. in view of Feola et al., U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier), Klatz et al., U.S. Pat. No. 5,395,314 (3/95: file 6/93 or earlier) and Hunter, U.S. Pat. No. 5,152,979 (10/92).

The discussion of the teaching of the Stamler et al. reference in the above rejection under 35 USC102/103 is hereby incorporated by reference in its entirety. To summarize, the Stamler et al. reference discloses the use of S-nitrosating agents (e.g. low molecular weight e.g. glutathione and hemoglobin derivatives) to treat disorders by achieving a variety of physiological effects including vasodilation; radical scavenging ; NO and oxygen delivery. The above reference does not explicitly disclose the use of nitrosating agent(s) to preserve living organs, treat malaria or sickle cell anemia. Feola et al. disclose the use of “blood substitutes” to restore blood volume, transport oxygen and reduce vasoconstriction (e.g. vasodilate) by the use of hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7). Hunter discloses that malaria is a blood disorder which results in ischemia caused by compromised microvasculature (e.g. see abstract and col. 1). Klatz et al. disclose a brain resuscitation and organ preservation composition which comprises perfluorocarbons which act as “a blood substitute” which “transport(s) oxygen in a manner similar to hemoglobin” (e.g. see Abstract, col. 1, col. 4, lines 1-25). The Stamler et al. reference provides the skilled artisan with motivation to use nitrosating agents alone or combined to treat disorders of diseases to which vasodilation and oxygen/NO transport would prove to be therapeutic. It would have been obvious to the skilled artisan at the time of applicant’s invention

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to utilize thionitrosating agents (e.g. hemoglobin, glutathione) as blood substitutes to treat blood disorders such as sickle cell anemia or malaria since the Feola reference discloses the use of hemoglobin and thiol containing blood substitutes to treat anoxic blood disorders (e.g. sickle cell anemia as disclosed by Feola and malaria as disclosed by Hunter) and Stamler provides a reasonable expectation that nitrosating agents will be successful to achieve the desired effects of blood substitutes. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize nitrosating agents for organ preservation since the Katz reference provides motivation to utilize compositions such as perfluorocarbons for their ability to act as "blood substitutes" and hemoglobin oxygen transporters and Stamler teaches that nitrosating agents would be successful to achieve the desired effects of blood substitutes and also act as effective hemoglobin oxygen transporters.

**General information regarding further correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 13, 1997



CECILIA J. TSANG  
SUPERVISORY PATENT EXAMINER  
GROUP 1800